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(67) LHRH analogs.

(67) The present invention deals with LHRH analogues which contain cytotoxic moieties and have influence on the release of gonadotropins from the pituitary gland of mammals, including humans. The compounds of this invention are represented by the formula:

X-R<sup>1</sup>-R<sup>2</sup>-R<sup>3</sup>-Ser-R<sup>5</sup>-R<sup>6</sup>(Q)-Leu-Arg-Pro-R<sup>10</sup>-NH<sub>2</sub>

wherein

R<sup>1</sup> is pGlu, Pro, D-Nal(2), or D-Phe(4Cl),

R<sup>2</sup> is His or D-Phe(4Cl),

R<sup>3</sup> is Trp, D-Trp or D-Pal(3),

R<sup>5</sup> is Tyr or Arg,

R<sup>6</sup> is D-Phe or R<sup>6</sup>, where R<sup>6</sup> is D-Orn, D-Lys or D-Phe(NH<sub>2</sub>),

R<sup>10</sup> is Gly or D-Ala,

X is hydrogen, a lower alkanoyl group of 2-5 carbon atoms or carbamyl,

Q is bis-(2-chloroethyl)amino group provided that R<sup>6</sup> is D-Phe,

where R<sup>6</sup> is R<sup>6</sup>,

Q is a complexed metal-containing acyl group having the formula:

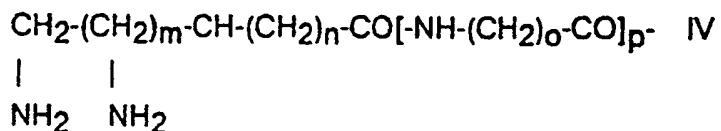


II III

wherein

Q' is Pt(Y)<sub>2</sub>, where Y is an anion derived from a pharmaceutically acceptable acid,

A is a diaminoacyl group having the formula



where

m is 0 or 1,

n and p are 0-10,

o is 1-10,

Q' is a non-platinum-group metal, either a main-group metal such as gallium, germanium, and tin, or a transition metal such as titanium, vanadium, iron, copper, cobalt, gold, nickel, cadmium and zinc,

B is a aralkylidene, heteroaralkylidene, cycloalkylidene or heterocycloalkylidene group containing oxygen anion or carboxylate anion at position 2 or 3, and pharmaceutically acceptable salts thereof and methods of use pertaining these compounds.



**EUROPEAN SEARCH  
REPORT**

EP 89 11 8460

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages		
A	INT. J. PEPT. PROT. RES., vol. 32, no. 1, 1988, pages 56-63; A. RICOUART et al.: "Photosubstitution of cysteine-trenylalanine as a tool in peptide chemistry" * Pages 56-57, column 1 *	1,5-10	C 07 K 7/20 A 61 K 37/43
D,A	CHEMICAL ABSTRACTS, vol. 94, 1981, page 49, abstract no. 11195j, Columbus, Ohio, US; K. CHANNABASAVAIH et al.: "New potent agonist and antagonist analogs of luteinizing hormone releasing hormone", & PEPT., STRUCT. BIOL. FUNCT., PROC. AM. PEPT. SYMP., 6TH 1979, 803-6	1-4	
A	J. ENDOCRINOL. INVEST., vol. 11, 1988, pages 535-567; B.J.A. FURR et al.: "Luteinizing hormone-releasing hormone and its analogues: a review of biological properties and clinical uses" * Page 540, column 2 - page 544, column 1 *	1-10	
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 86, no. 16, August 1989, pages 6313-6317, Washington, DC, US; S. BAJUSZ et al.: "Highly potent metallopeptide analogues of luteinizing hormone-releasing hormone" * Entire article *	1,5-10	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 86, no. 16, August 1989, pages 6318-6322, Washington, DC, US; S. BAJUSZ et al.: "Highly potent analogues of luteinizing hormone-releasing hormone containing D-phenylalanine nitrogen mustard in position 6" * Entire article *	1-4	C 07 K A 61 K
The present search report has been drawn up for all claims			
Place of search	Date of completion of search	Examiner	
The Hague	28 November 90	GROENENDIJK M.S.M.	
CATEGORY OF CITED DOCUMENTS			
X: particularly relevant if taken alone		E: earlier patent document, but published on, or after the filing date	
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T: theory or principle underlying the invention		S: member of the same patent family, corresponding document	

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